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Metformin or Antiandrogen in the Treatment of Hirsutism in Polycystic Ovary Syndrome

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Hirsutism is a common and distressing symptom frequently encountered in women with polycystic ovary syndrome (PCOS), who also show relative insulin resistance. The aim of this trial, in which hirsutism was the primary end point, was to compare the efficacy of the oral antihyperglycemic medication metformin with that of an established treatment, combined ethinyl estradiol and cyproterone acetate. Patients (n = 52) were randomized to receive either metformin (500 mg, three times daily) or Dianette (ethinyl estradiol, 35 μg; cyproterone acetate, 2 mg) treatment for 12 months, with assessments before treatment, at 6 months, and at 12 months. Both objective and subjective methods of evaluating hirsutism were used, and in addition, patient perceptions were examined. The results show that metformin is potentially an effective treatment for moderate to severe hirsutism in women with PCOS. They also suggest that in some respects (Ferriman-Gallwey score and patient self-assessment), it is more efficacious than the standard treatment (Dianette). The objective evaluation of hair diameter reduction showed that both treatments were moderately effective at multiple anatomical sites. Dianette treatment was responsible for profound suppression of androgen activity, in contrast to metformin, which induced negligible change. However, metformin did reduce markers of insulin resistance. The data suggest that hirsutism may be effectively treated by reducing hyperinsulinemia. (*J Clin Endocrinol Metab* 88: 4116–4123, 2003)

HIRSUTISM IS EXCESSIVE hair growth in a male pattern distribution in women. It is not only distressing to patients, but also presents a challenging clinical management dilemma. In approximately 90% of women with hirsutism, the underlying disorder is either polycystic ovary syndrome (PCOS) with its intrinsic hyperandrogenism or is idiopathic, related to increased tissue sensitivity to androgens (1). In fact, a high proportion of patients with idiopathic hirsutism demonstrate polycystic ovaries (2), suggesting that these two forms may not be easily distinguished.

PCOS is a heterogeneous disorder characterized by chronic anovulation, hyperandrogenism, and hyperinsulinemia secondary to reduced insulin sensitivity. The increased secretion of ovarian androgens is considered to be due to increased insulin stimulation of ovarian steroid-secreting cells by insulin itself and also insulin-stimulated growth factors, including IGF-I, and decreased IGF-binding protein (IGFBP) activity (3). Hyperandrogenism commonly manifests itself as hirsutism (60–83%), acne (11–43%) (4), seborrhea, and alopecia.

Androgens have been shown to be at least partly responsible for promoting the anagen phase (growth phase) of the hair cycle, leading to larger hair follicles (5) and bringing about a change from vellus to terminal hair status. *In vitro* studies show that the active androgen is 5α-dihydrotestosterone, produced locally by the action of 5α-reductase enzyme on testosterone (1). The anagen phase has also been shown to be influenced by the growth factor, IGF-I. IGF-I is carried in the circulation, predominantly by specific IGFBPs, but it is also produced locally by the dermal papilla, where it acts on both the dermis and epidermis (6, 7). The activity of these growth factors depends on a number of factors, including local and circulating binding proteins, which, in turn, are also influenced by the actions of insulin. Thus, women with PCOS may demonstrate abnormalities in the metabolism of both of the major factors responsible for hirsutism: androgens and insulin/growth factors.

Women with PCOS suffer from a high incidence of acne, which has also been linked with raised serum androgen (8), insulin (9), and IGF-I (10) concentrations in the circulation.

The use of oral antihyperglycemic medication (OAM), predominantly metformin and the thiazolidenediones, in the treatment of women with PCOS, has been shown to improve insulin sensitivity and ovarian function. Treatment with the OAM metformin reduced circulating insulin, LH, androstenedione, and testosterone concentrations in a number of studies, and protracted treatment has resulted in improvements in body mass index (BMI), menstrual cycle regulation, spontaneous ovulation rates, and spontaneous and assisted pregnancy rates (11–13). It has been hypothesized that by reducing circulating insulin concentrations, leading to decreased free androgen concentrations, OAMs may ameliorate hirsutism. In fact, examination of the literature shows that most, but not all, controlled studies achieved modest reductions in circulating free androgens using metformin (13). A recent study in lean women with PCOS showed significant reductions of circulating testosterone, even though they were only modestly elevated before treatment (14). However, changes in insulin and possibly IGF metabolism justify further examination of this therapeutic approach, because, as described above, changes in the growth

Abbreviations: BMI, Body mass index; CL, confidence limits; CV, coefficient of variation; DHEAS, dehydroepiandrosterone sulfate; FG, Ferriman-Gallwey; HOMA-IR, homeostasis assessment for insulin resistance; IGFBP, IGF-binding protein; OAM, oral antihyperglycemic medication; PCOS, polycystic ovary syndrome.

factor environment may also be important in the treatment of hirsutism.

Some recent reports have addressed the use of OAMs in hirsutism (15–20). However, in none of them was hirsutism a primary outcome measure, and no objective measure of hair growth was undertaken. There has been one very small study reporting the effect of metformin on hirsutism as a primary end-point measure and using an objective measure of hair growth (21). The results suggested that metformin may show benefit compared with placebo.

The aim of this trial, in which hirsutism is the primary end point, was first to elucidate whether metformin does have an effect on hirsutism in women with PCOS, and second to compare its efficacy with an established treatment for hirsutism, combined ethinyl estradiol and cyproterone acetate. In doing so we have used objective techniques, validated subjective methods of assessment of hirsutism, and incorporated patient perception measures.

Subjects and Methods

Study population

Women with PCOS (n = 52), whose primary complaint was hirsutism [Ferriman-Gallwey (FG) score, >8] were recruited from the Reproductive Endocrinology clinic at the Royal Infirmary (Glasgow, UK). The diagnosis of PCOS included at least two of the three following features: oligomenorrhea/amenorrhea, polycystic ovaries on ultrasound (2), or an elevated free androgen index. Exclusion criteria included contraindications to either metformin or Dianette (including BMI >38) and use of oral contraception or metformin within the previous 3 months. None had thyroid dysfunction, hyperprolactinemia, diabetes mellitus, or late-onset congenital adrenal hyperplasia. Women taking medication known to affect gonadal or adrenal function, or carbohydrate or lipid metabolism were also excluded. Women were also advised to use barrier contraception if randomized to metformin.

Informed consent was obtained from each woman, and the study was conducted at the Royal Infirmary after obtaining approval from the ethics committee of the North Glasgow Hospitals University National Health Service Trust.

Study design

Treatments. Patients were block-randomized (n = 10/block) in a 1:1 ratio to receive either ethinyl estradiol (35 μg) and cyproterone acetate (2 mg; Dianette, Schering AG, Berlin, Germany) or metformin (Glucophage, Merck, West Drayton, UK) for a 12-month treatment course. Randomization was by random number tables. The patient number treatment codes were held by a third party and were allocated individually after obtaining written consent. A list of codes was kept by a third party, and patient names were checked after completion of the trial. Medication was commenced 1 wk after obtaining written consent. Dianette was administered in the recommended regimen (35 μg ethinyl estradiol plus 2 mg cyproterone acetate, 21 d/month, followed by a 7-d pill-free period). Metformin (metformin hydrochloride) was administered orally at a dose of 500 mg, three times daily.

Assessment program. At baseline (T0), 6 months (T6), and 12 months (T12), all patients underwent clinical and hormonal assessments. These included anthropometric measurements of height, weight (BMI), waist/hip ratio, blood pressure, and hirsutism using the FG score and hair diameter measurements. These assessments were performed by the same trained observer (L.H.). The sebum excretion rate was also assessed at each time point, and a side-effect profile was performed at 2, 6, and 12 months. Assessment of patient perception was recorded at 0, 6, and 12 months for hirsutism and acne. Circulating concentrations of insulin, glucose, testosterone, SHBG, androstenedione, dehydroepiandrosterone sulfate (DHEAS), 17α-hydroxyprogesterone, cholesterol, triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol, IGF-I, and IGFBP-3 were also determined in a fasting blood sample taken at T0, T6, and T12.

Methods

BMI was calculated using the equation: weight (kilograms)/height (meters)^2. The data were subgrouped for analysis of the impact of BMI on responses using the median value for the study population (BMI = 34).

Waist and hip circumferences were measured to the nearest centimeter with a soft tape according to WHO criteria.

Blood pressure measurements were performed manually using a sphygmomanometer in a standard clinical method. The heart sound Korotkoff 4 was taken to ascertain diastolic measurement. Where BMI was raised, a large cuff was used.

Hirsutism was assessed clinically, using the modified FG method (22) carried out by the same researcher (L.H.). A value greater than 8 was considered hirsute. The FG score has been shown to be reproducible to a level of three points (23).

Hair diameter values were obtained from samples of terminal hair collected from the chin, abdomen, anterior midthigh, and forearm of each patient using a stitch cutter blade (Swann-Morton) to cut flush with the skin. Multiple hairs from each site were fixed on a microscope slide with the hair base to one end. Diameters were determined using digital image analysis software (Image Pro Plus, Media Cybernetics, Silver Spring, MD), with the calipers set in a vertical frame, perpendicular to the axis of the hair. The section measured was adjacent to the hair base, thus representing most recent hair growth. One investigator (L.H., blinded to treatment group) made all hair diameter measurements, and the method technical error (multiple measurements of the same hair) was less than 1% at a mean diameter of 86 μm. The variability of hair diameter within any one site was determined to be 16%. Mean hair diameters were calculated by averaging the values from each anatomical site (where possible, six hairs were used to calculate the site average) and calculating a mean of the site averages per case.

Forehead sebum excretion rate tests were performed following standard methods (24). This involved fixing blotting paper in contact with the forehead for 90 min, after which, a chemical extraction of sebum with diethyl ether was performed, and the dried sebum was weighed (expressed as milligrams per square meter per hour).

Analytes: assay methods

Hormone concentrations were assayed in patient-specific batches to eliminate the effect of interassay drift. Testosterone was assessed using the semiautomated Immulite technology (Diagnostic Products, Los Angeles, CA), whereas SHBG, DHEAS, IGF-I, and IGFBP-3 were assessed with the Immulite 2000 analyzer (Diagnostic Products). Androstenedione and 17α-hydroxyprogesterone were assayed using in-house RIAs [intraassay coefficients of variation (CVs), both <12%].

Plasma glucose was measured using the glucose oxidase method (Advia 1650 Chemistry System, Bayer, Leverkusen, Germany; intraassay CV, <2%), and insulin was measured using a competitive RIA (in-house; intraassay CV, <8%).

Homeostasis assessment for insulin resistance (HOMA-IR) was calculated from the fasting concentrations of insulin and glucose using the following formula: HOMA-IR = fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/liter)/22.5.

Plasma total cholesterol, triglyceride, and high density lipoprotein cholesterol measurements were performed using a modification of the standard Lipid Research Clinics protocol (25) with the Bayer Advia 1650 Chemistry System (intraassay CV, <2%).

Questionnaires

Patients were asked to assess their own status of hirsutism and acne, and the effects of treatment at T0, T6, and T12. This was estimated in a quantitative manner, using a mark on a visual analog sliding scale. In the same questionnaire, they were asked to assess change in hair quality and their need for use of cosmesis (*i.e.* methods of hair removal) at T6 and T12, using Boolean operators.

A side-effect profile questionnaire was completed after 2 months (T2), at T6, and at T12 to assess worsening of symptoms compared with

baseline, using Boolean operators. Issues covered included reduced appetite, nausea, vomiting diarrhea, headache, breast tenderness, and depression.

Statistics

Changes in parameters over time were assessed using repeated measures ANOVA, and differences between groups were evaluated using a nonparametric test (Mann-Whitney). Comparisons between two time points within the same patient were effected using paired *t* tests. Proportions of patients responding were compared using contingency table analyses.

Results

Patients and randomization

The baseline characteristics of the two treatment groups were similar. The mean age of the Dianette group was 31.7 yr [95% confidence limits (CL), 26.8–36.5 yr], and that of the metformin group was 31.3 yr (CL, 27.9–34.7). Normal (nonhirsute) values for the FG score are less than 8, so the degree of hirsutism in both groups was considerable, with the Dianette group showing a mean value of 22.8 (CL, 19.7–26.0) and the metformin group a mean of 20.3 (CL, 17.8–22.9; group difference, $P = 0.24$). The patients were generally obese (mean BMI, 31.8 and 31.7 for Dianette and metformin, respectively), and the proportions of patients in each group with BMI greater than 29 were: Dianette, 20 of 26; and metformin, 14 of 26. Elevated fasting insulin concentrations in the circulation were observed (laboratory upper limit of normal, 13.9; mean values of 19.0 and 15.8 for Dianette and metformin, respectively; $P = 0.92$), and the proportions patients showing elevated fasting insulin were: Dianette, 8 of 26; and metformin, 9 of 26. Fasting glucose concentrations were within the normal range. The free androgen index (normal upper limit, 7.9) was elevated in both groups (mean values: Dianette, 15.8; metformin, 14.1), and the proportions of patients in each group with a free androgen index above 7.9 were: Dianette, 16 of 26 (62%); and metformin, 14 of 26 (54%). Acne was generally not a profound problem among the groups.

Figure 1 shows the process of patients from recruitment and randomization and through the 12-month treatment program. There were more patients discontinuing Dianette (n = 10) than metformin (n = 8, including three pregnancies) and for a greater variety of reasons (no significant difference between the groups).

Hirsutism

Figure 2 shows that the FG score was significantly reduced after treatment in both groups, using repeated measures ANOVA. The degree of reduction in FG score was significantly greater ($P < 0.01$, by Mann-Whitney test) in the metformin group (~25%) compared with the Dianette group (~5%). Twelve months of treatment with metformin resulted in five patients with severe hirsutism (FG score, ≥15 at T0) achieving a FG score of less than 15 (*i.e.* moderate/mild hirsutism) of a total of 22, whereas only one did so after Dianette treatment (of 25; $P = 0.08$, by χ^2 test).

The mean hair diameters were significantly reduced ($P \leq 0.001$, by repeated measures ANOVA) in both groups during the treatment program (Fig. 3) and to a similar degree (Dianette, 17% reduction; metformin, 12%; difference between groups, $P = 0.15$). Table 1 shows changes in hair diameter according to anatomical site. In fact, the changes in hair diameter appeared to be dependent upon either anatomical site and/or baseline hair diameter in both treatment groups. It can be seen that hairs on the forearm were relatively fine at T0 and underwent negligible change, whereaas hairs on the chin and abdomen were relatively coarse at T0 and underwent considerable change (both groups).

Patient self-assessments

Table 2 shows that patient self-assessment (visual analog scale) of both hirsutism (Fig. 4) and acne underwent signif-

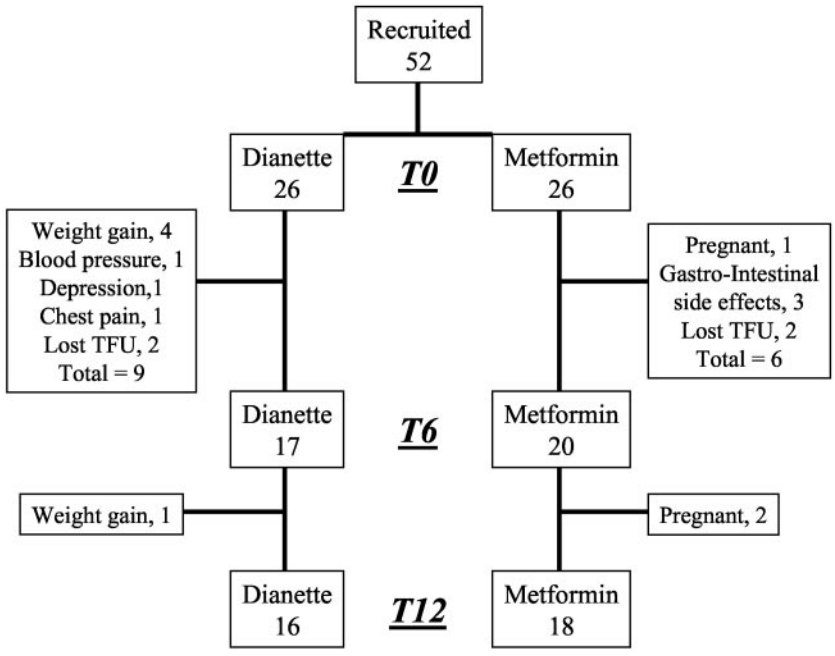

FIG. 1. Randomization and process of patients from recruitment to completion of treatment after 12 months with Dianette or metformin. Lost TFU, Lost to follow-up.

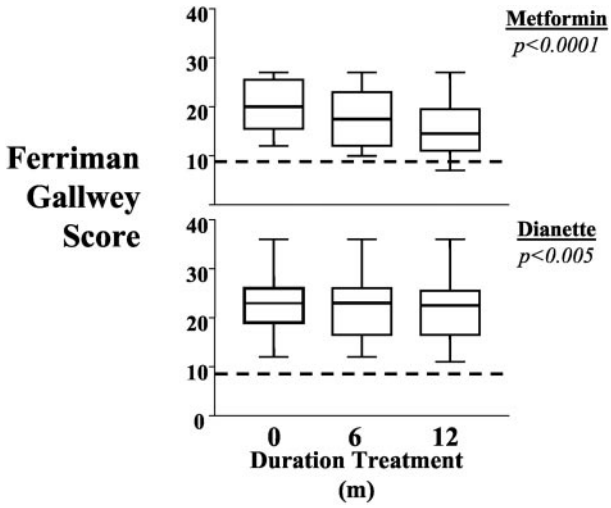

FIG. 2. FG score assessment of hirsutism through the program of treatment with Dianette or metformin over 12 months. The *broken line* represents the upper limit of normal values.

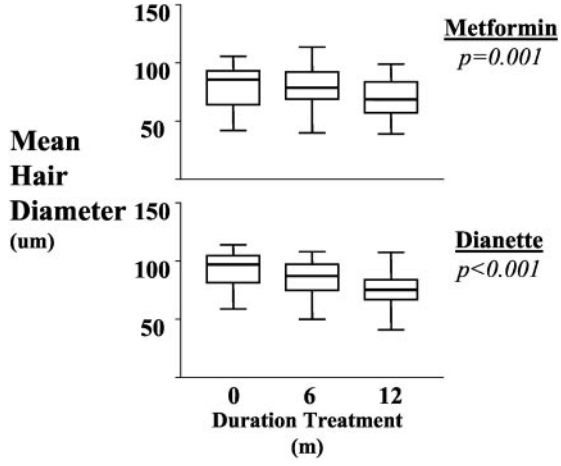

FIG. 3. Mean terminal hair diameter values through the program of treatment with Dianette or metformin over 12 months.

TABLE 1. Changes in mean hair diameter according to anatomical site during 12 months treatment with Dianette or metformin

	Dianette				Metformin			
	T0	T12	%	*P*	T0	T12	%	*P*
Chin (μm)	115	102	11	0.06	103	91	12	0.09
Abdomen (μm)	100	75	25	0.0004	93	72	22	0.002
Mid-thigh (μm)	89	71	20	0.0001	67	62	8	0.10
Forearm (μm)	63	58	8	0.03	53	52	2	0.38
Combined (μm)	92	76	17	0.001	79	69	13	0.004

The data were compared using paired *t* test analyses.

icant reduction in both groups (by ANOVA). There was no difference between the treatment groups at T0, but at T12 the metformin patients scored their hirsutism significantly lower than the Dianette group (by Mann-Whitney test, $P = 0.01$).

Table 3 demonstrates changes in patient perception of specific qualitative aspects of their hirsutism. More than half of the patients in both treatment groups assessed their hair quality to be finer after treatment, and there was no difference between the treatments in this parameter. Approximately half of the metformin group recorded that their hair growth rate was reduced at T6. This proportion was significantly ($P < 0.05$) greater than that in the Dianette group. Half of the metformin-treated patients responded with a reduced requirement for the use of cosmesis (T6 and T12). This proportion was not significantly greater than the Dianette group at either time point. The overall appearance as a description specific to hirsutism was improved in more than 50% at both T6 and T12 in the metformin group. This was a significantly greater proportion than in the Dianette group at both time points.

Acne and sebum excretion

The degree of acne in general was low (secondary outcome measure), but both groups believed that acne improved significantly (Table 2) by self-assessment. There was no difference between the treatment groups in the responses recorded ($P = 0.36$).

The sebum excretion rates underwent modest improvement ($P < 0.05$) during Dianette treatment, but no change during metformin treatment [Dianette, from 0.14 $\mu g/m^2 \cdot h$ at T0 to 0.08 at T12 ($P = 0.04$); metformin, 0.15 $\mu g/m^2 \cdot h$ at T0 to 0.12 at T12 ($P = 0.18$)].

Hormone changes

The effects of Dianette treatment on hormone profiles at 6 and 12 months were profound (Table 4), with reduced total androgens in the circulation and an increase in the SHBG, effectively reducing free androgen levels to values below the normal range. Similar changes were recorded in circulating 17α-hydroxyprogesterone and DHEAS. However, there was no effect on glycemic parameters, and the BMI did not change over the 12-month course of treatment. In contrast, metformin treatment showed negligible effects on circulating total androgens, SHBG, free androgen index, or 17α-hydroxyprogesterone, although a significant ($P = 0.02$) increase in circulating DHEAS was observed. However, metformin treatment resulted in a significant decrease in the glucose/insulin ratio and the logHOMA-IR, suggesting improved efficiency of utilization of glucose secondary to improved insulin sensitivity. There was no change in the circulating IGF-I, IGFBP-1, or IGFBP-3 during metformin treatment.

Blood pressure and circulating lipid profiles during metformin treatment

Table 4 shows that Dianette treatment was not associated with changes in blood pressure, whereas the patients treated with metformin showed a clinically insignificant increase in diastolic blood pressure. There was no change in systolic blood pressure in either treatment group. The circulating lipid profiles were normal and showed nonsignificant improvements during treatment with metformin (Table 4).

Changes in hirsutism and metformin treatment

Metformin treatment was associated with changes in the FG scores, BMI, and improved indexes of insulin action.

TABLE 2. Comparison of patient's own quantitative self-assessments of hirsutism and acne through and at the end of 12-month treatment with either Dianette or metformin

	Dianette				Metformin				Mann-Whitney *U* test
	T0	T6	T12	ANOVA (*P*)	T0	T6	T12	ANOVA (*P*)	Rx Groups T12
Hirsutism	7.4	7.1	6.6	0.005	7.0	5.0	3.9	<0.0001	0.01
Acne	2.0	1.2	1.0	0.002	3.4	2.9	1.9	0.005	0.36

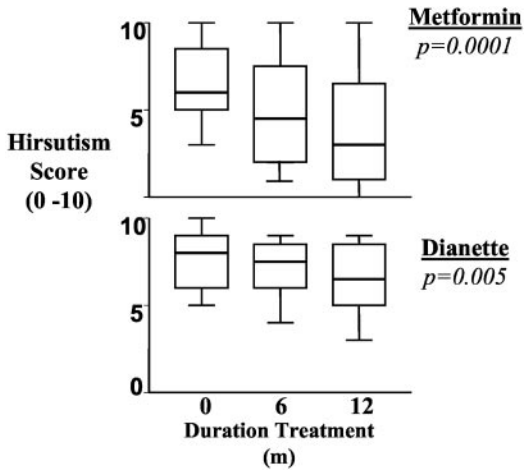

FIG. 4. Self-assessment scores through the program of treatment with Dianette or metformin over 12 months.

There was little correlation among these specific changes. Those individuals who lost more than one BMI point (n = 11) showed no greater reduction in FG score (reduction of 3.8 FG units) compared with those who lost less weight (n = 7; reduction of 6.6 FG units, $P = 0.13$). Similar analyses with the glucose/insulin ratio showed that those showing the greatest improvement in the ratio reduced their FG scores to the same degree as those showing a relatively inferior response (mean FG reductions, 4.8 and 5.0, respectively).

The changes in FG score showed poor correlations with changes in glucose/insulin ratio and logHOMA-IR value (glucose/insulin, $r^2 = 0.01$; change in HOMA-IR, $r^2 = 0.004$), indicating that changes in hirsutism were relatively independent of changes in both measures of insulin sensitivity. The correlation of change in FG score with change in BMI ($r^2 = 0.17$) was not significant ($P = 0.08$).

The population median BMI was 34, and responses were examined according to the two BMI subgroups (n = 9 each) lying to either side of this value. The data suggest that BMI may be a relevant factor with respect to treatment efficacy as the leaner subgroup showed a tendency ($P = 0.08$) to greater improvement in FG score (6.8 U; 95% CL, 3.3–10.3) than the more obese subgroup (3.0 U; 95% CL, 0.2–6.2). The same subgrouping revealed that the change in the free androgen index was significantly greater ($P = 0.03$) in the leaner subgroup.

A similar examination of changes in FG score in relation to hyperandrogenemia before treatment (free androgen index, >7.9) failed to establish any relationship, as both groups showed similar FG scores at T0 and T12, with similar degrees of benefit.

Side effects

Table 5 shows the results of side effect recordings by those patients who continued on each treatment despite side effects. It shows that the side effect profiles of both treatments were moderate, and there was little difference between the treatment groups. Gastrointestinal problems (including reduced appetite) affected approximately half of the patients on metformin in the first 6 months, contrasting with the Dianette group. Headache and breast tenderness were features in both treatment groups, but there was no difference between them.

Discussion

The results of this prospective, randomized, controlled study show that metformin is an effective treatment for moderate to severe hirsutism in women with PCOS. The data also suggest that in some respects (FG score and patient self-assessment), it is more efficacious than the gold standard treatment, combined estrogen and antiandrogen (cyproterone acetate), Dianette. The objective evaluation of one component of hirsutism, hair diameter, showed that both treatments were effective in reducing mean diameters at multiple anatomical sites. However, this reduction was modest in both treatment groups.

To our knowledge, this is the first comparative, randomized, controlled trial of sufficient duration and patient number to address the issue of efficacy and acceptability of metformin, in the treatment of hirsutism in women with PCOS, as a primary outcome measure. Furthermore, the use of an objective measure of one aspect of hair growth is an important addition to the assessment, as subjective evaluations may be influenced by many factors.

Previous trials addressing the use of OAMs for the treatment of hirsutism in women with PCOS were not unanimous, but four of them suggested that metformin treatment would be efficacious if addressed directly. However, the studies generally suffered from small patient number, patients who were only mild to moderately hirsute (assessed by FG score), and short therapeutic duration, and only one study employed an objective measure of hair analysis. In none of the trials was treatment acceptability or assessment of response explored.

Our trial indicates that the recorded improvement in hirsutism also equated with patient perception of improvement, which was strongly in favor of metformin compared with Dianette. The acceptability of metformin as a treatment for hirsutism appeared to be high. In addition, although side-effects were similar in the two treatment groups, there was a trend toward increased compliance in the metformin group, as evidenced by a lower side effect-motivated drop-

TABLE 3. Proportions (presented as %) of patients reporting changes in qualitative aspects of hirsutism after 6-month (T6) and 12-month (T12) treatment with Dianette or metformin

	T6 (%)			T12 (%)		
	Dianette	Metformin	*P*	Dianette	Metformin	*P*
Finer hair quality	59	56	ns	65	61	ns
Reduced rate of hair growth	24	56	0.02	65	44	ns
Reduced need for cosmesis	18	50	0.08	25	50	ns
Overall improved appearance (hirsutism)	6	55	0.002	25	61	0.002

ns, Not significant.

TABLE 4. Changes in mean circulating hormone concentrations and anthropomorphic features over 6 and 12 months of treatment with either Dianette or metformin

	Dianette			*P*	Metformin			*P*
	T0	T6	T12		T0	T6	T12	
Fasting insulin (mU/liter)	16.5	14.5	15.0	0.7	15.8	12.0	11.3	0.07
Glucose (mmol/liter)	5.0	4.8	4.8	0.3	5.4	5.2	5.3	0.5
logHOMA-IR	0.49	0.39	0.44	0.35	0.49	0.37	0.32	0.03
Glucose/insulin	0.40	0.50	0.40	0.2	0.45	0.55	0.68	0.004
Testosterone (nmol/liter)	3.52	2.38	2.68	0.006	3.19	3.34	2.82	0.39
SHBG (nmol/liter)	31.4	141.1	117.4	<0.0001	30.4	29.6	28.8	0.90
FAI	15.5	2.0	3.2	<0.0001	14.1	15.5	12.9	0.4
DHEAS (μmol/liter)	7.2	4.8	4.4	0.0002	6.8	7.9	7.4	0.02
Androstenedione (ng/ml)	11.6	7.7	8.2	0.0001	11.6	11.5	10.4	0.3
17αOH Progesterone (nmol/liter)	5.4	2.3	3.1	0.0008	4.2	5.2	5.8	0.2
BMI	31.8	31.1	31.3	0.15	31.7	30.3	30.1	0.001
WHR	0.81	0.81	0.81	0.69	0.85	0.84	0.85	0.59
BP: diastolic (mm Hg)	73.1	73.4	72.8	0.97	74.4	76.4	80.3	0.01
BP: systolic (mm Hg)	118.8	116.3	116.3	0.58	119.1	117.2	120.4	0.71
Cholesterol (total: mmol/liter)	4.90	5.05	4.75	0.35	4.98	4.87	4.79	0.32
Triglycerides (mmol/liter)	1.68	1.68	1.54	0.72	1.48	1.24	1.27	0.19
LDL Cholesterol (mmol/liter)	2.81	2.43	2.55	0.40	3.08	2.94	2.85	0.39
HDL Cholesterol (mmol/liter)	1.41	1.64	1.51	0.01	1.29	1.27	1.31	0.52
IGF-I (ng/ml)					267	250	250	0.90
IGFBP-1 (ng/ml)					21.6	32.2	25.9	0.30
IGFBP-3 (ng/ml)					6.6	6.5	6.4	0.50

FAI, Free androgen index; WHR, waist/hip ratio; BP, blood pressure.

out rate (excluding pregnancies). This is important, as high patient compliance is essential for optimal treatment effect, given the length of time of the hair biocycle.

Overall, the results present a counterintuitive profile in the observations of a limited change in circulating total and free androgens at the same time as considerable improvements in hirsutism. Hirsutism is a result of end-organ sensitivity as well as direct androgen stimulation, and this tissue sensitivity is known to be controlled by factors other than androgens, such as insulin and IGF-I activity. In our study metformin treatment showed significant improvement in the glucose/insulin ratio and the logHOMA-IR, but it had negligible impact on circulating androgens. In contrast, Dianette virtually eliminated free androgens from the circulation, but, in fact, showed little effect on severe hirsutism, as has been recorded previously (4). Taken together, these data suggest that addressing insulin insensitivity may be a more effective therapeutic approach to hirsutism in women with PCOS than aggressive suppression of androgens in the form of antiandrogen therapy. Thus, hirsutism and hyperandrogenism may be related through a common underlying mechanism in addition to a direct androgen stimulant-response etiology.

The activity of IGF-I is related to both absolute circulating concentrations and those of its carrier proteins, such as IGFBP-3, which effectively reduce IGF potency. Women with PCOS may have raised circulating free IGF-I, mediated mainly through reduced IGFBPs, suggesting increased growth factor stimulation (26, 27). However, we did not demonstrate any change in the circulating concentrations of IGF-I, IGFBP-3, or IGFBP-1 after metformin treatment; thus, we may hypothesize that the beneficial effect of metformin is unlikely to be due to an effect on circulating growth factor stimulation. Correspondingly, benefit may be due to a mechanism involving local growth factor action at the dermal papillae. The inability of metformin to decrease serum IGF-I concentrations has been reported previously (28, 29).

The failure of metformin to influence circulating SHBG concentrations beyond placebo or control is another surprising observation that has been recorded previously (13). The pretreatment values would be considered low and representative of a cohort of obese women with PCOS. The failure to significantly change these values with protracted treatment may reflect the confounding effect of obesity in the patient cohort and the complex nature of SHBG control mechanisms. Body mass has a profound influence on SHBG secretion. The weight loss during the program was modest, and the patients remained generally obese. It may be that a greater degree of weight loss is needed to effect a substantial increase in SHBG, such that higher doses of metformin should be used in obese women.

TABLE 5. Record of side effects considered attributable to either treatment with Dianette or metformin at 2 months (T2), 6 months (T6), and 12 months (T12)

	Time	Dianette (%)	Metformin (%)	*P*
Reduced appetite	T2	2	46	0.004
	T6	0	60	0.001
	T12	0	33	0.001
Nausea	T2	27	23	ns
	T6	6	25	ns
	T12	0	17	ns
Vomiting	T2	8	8	ns
	T6	12	0	ns
	T12	0	0	ns
Diarrhea	T2	8	50	0.002
	T6	6	45	0.01
	T12	0	33	0.02
Headache	T2	30	16	ns
	T6	18	10	ns
	T12	19	17	ns
Breast tenderness	T2	38	15	ns
	T6	35	30	ns
	T12	25	17	ns
Depression	T2	23	8	ns
	T6	24	20	ns
	T12	6	17	ns

ns, Not significant.

We observed poor correlations between reduction in FG score and changes in BMI or measures of insulin sensitivity, suggesting that neither of these changes is directly responsible for improvement in FG score, further suggesting that beneficial effects may be due to endocrine changes not yet determined, such as the evolution of growth factor and binding protein complexes at the local tissue level, secondary to induced changes in insulin sensitivity.

The degree of acne in our patient cohort was generally low, and it is difficult to extract useful conclusions from the data, as there was no absolute difference between the two treatment groups for sebum excretion over the 12 months. This is probably related to the fact that acne was not a primary complaint in our study.

The examination of the impact of morbid obesity on the responses to metformin therapy suggest that in such women metformin at a dose of 500 mg, three times daily, may have reduced efficacy compared with that in leaner women. A similar observation was recorded with morbidly obese women with PCOS in aspects of improving ovarian function, weight reduction, and circulating lipids (30). This observation suggests that either morbidly obese women are refractory to metformin therapy or, quite simply, that the current dose is insufficient.

Lifestyle change and weight loss have been shown to be effective means of treating many of the abnormalities associated with PCOS (31, 32), and hirsutism may respond to this approach. Crave *et al.* (33) suggested that metformin may confer no additional advantage over weight loss, which contrasts with the analyses presented above.

In summary, the results of this study open the prospect of a realistic treatment for a large number of women with hirsutism and PCOS, and possibly also idiopathic hirsutism, a large proportion of whom (>90%) have polycystic ovaries (2). The beneficial effects do not appear to be mediated by suppression of circulating androgens, which makes it possible that hyperinsulinemia or related metabolic pathways may be important determinants of end-organ responses at the level of the hair follicle. Future work should address this therapeutic approach through examining optimal doses of OAMs, either alone or in combination with antiandrogen treatment.

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